Protocol design and synopsis: Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy (OUtMATCH)

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Background: Food allergy is common and causes substantial morbidity and even mortality. Safe and effective treatments for food allergy would therefore be highly desirable, especially for individuals with multiple food allergies.

Objectives: Our aim was to describe a phase 3 study on treatment of patients with multiple food allergies with omalizumab.

Methods: The study was developed as a collaboration between the Consortium for Food Allergy Research, the National

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Institute of Allergy and Infectious Diseases, and 2 industry sponsors (Genentech and Novartis).
Results: The study is currently under way, enrolling participants from age 1 year to age 55 years who are allergic to peanut and at least 2 other foods (including milk, egg, wheat, cashew, hazelnut, and walnut). The study is designed to address 3 major questions. First, stage 1 will study the potential value of omalizumab for the treatment of patients with peanut allergy and at least 2 other common food allergens. Second, stage 2 will directly compare treatment of patients with multifood allergies using omalizumab as monotherapy versus treatment with omalizumab-facilitated multiallergen oral immunotherapy in which omalizumab is used as an adjunctive treatment. Third, stage 3 will address the longer-term outcomes following these treatment approaches, including the introduction of dietary forms of the study foods to induce or maintain desensitization.
Conclusions: This phase 3 study will provide important information on the potential of omalizumab to treat patients with multiple food allergies. (J Allergy Clin Immunol Global 2022;1:225-32.)

Key words: *Food allergy, immunotherapy, immunomodulator, omalizumab*

Food allergy affects approximately 32 million Americans.[1] It causes substantial morbidity and mortality and is the most common cause of anaphylaxis in pediatric patients. Successful avoidance of offending foods can be extremely difficult, particularly for patients with allergy to multiple foods (herein referred to as "multifoods"), with food allergy having a major negative impact on quality of life and a significant burden on our health care system, with an estimated cost of approximately $25 billion annually.[2] The burden of food allergy in adults is recognized less often, but in reality most peanut and tree nut allergies persist into adulthood, as does a substantial subset of milk, egg, and wheat allergies.[3]

Since its initiation in 2005, the Consortium for Food Allergy Research (CoFAR) has worked to develop potential treatments for food allergy, including oral, subligual, and epicutaneous immunotherapy.[4-6] Although substantial progress has been made, including increased interest from Pharma and even a US Food and Drug Administration–FDA approved oral immunotherapy for peanut allergy, substantial gaps remain. The most important of these gaps include treatment for foods other than peanut and treatment of patients with allergy to multifoods while maximizing safety. The goal of this study is to address each of these substantial gaps, especially in patients with significant allergy to multifoods. This is clearly an unmet need, as 40% to 70% of children and adults with peanut allergy indeed have other food allergies as well.[7,8]

As described in detail in this article, this phase 3 study is designed to address 3 major questions. First, stage 1 will study the potential value of omalizumab for the treatment of patients with peanut allergy and at least 2 other common food allergens. If successful, this could lead to a major advance in the treatment of patients with multifood allergies, with the potential to provide effective therapy without the need for a food-specific treatment such as oral immunotherapy (OIT). Second, stage 2 will directly compare treatment of patients with multifood allergies using omalizumab as monotherapy versus treatment with omalizumab-facilitated multiallergen OIT in which omalizumab is used as an adjunctive treatment. Third, stage 3 will address the longer-term outcomes following these treatment approaches, including the introduction of dietary forms of these foods to induce or maintain desensitization.

Abbreviations used

AE:	Adverse event
CoFAR:	Consortium for Food Allergy Research
DAIT:	Division of Allergy, Immunology, and Transplantation
DBPCFC:	Double-blind placebo-controlled food challenge
EoE:	Eosinophilic esophagitis
IDE:	Initial dose escalation
NIAID:	National Institute of Allergy and Infectious Diseases
OFC:	Oral food challenge
OIT:	Oral immunotherapy
OLE:	Open label extension

METHODS

This is a multicenter, randomized, double-blind, placebo-controlled study of participants aged 1 year to 55 years with peanut allergy and at least 2 other food allergies (including milk, egg, wheat, cashew, hazelnut, and walnut allergy). Although a participant may have more than 2 other food allergies, just peanut and 2 other foods will be studied for each participant. As displayed in Fig 1, the study includes 3 distinct stages.

In stage 1, participants who experience dose-limiting symptoms in response to a single dose of no more than 100 mg of peanut protein (cumulative dose 144 mg) and no more than 300 mg of protein (cumulative dose 444 mg) for each of the other 2 participant-specific foods during screening double-blind, placebo-controlled food challenge (DBPCFC) are randomized 2:1 to receive 16 to 20 weeks of treatment with omalizumab or placebo injections. After 16 weeks of treatment, each participant repeats DBPCFC to each of their 3 foods and placebo, for a cumulative dose of 6044 mg of protein of each food.

The first 60 participants who complete stage 1 are assigned to a 24-week open label extension (OLE) of omalizumab, followed by DBPCFC to each of their 3 foods and placebo, for a cumulative dose of 8044 mg of protein of each food. These participants then proceed to stage 3, whereas all other participants who have completed stage 1 move to stage 2.

In stage 2, each participant receives 8 weeks of treatment with open label omalizumab, after which they are randomized 1:1 to double-blind treatment with either (1) omalizumab-facilitated OIT, consisting of open label omalizumab plus multiallergen OIT for 8 weeks followed by placebo plus multiallergen OIT for 44 weeks, or (2) omalizumab plus placebo OIT, consisting of open label omalizumab plus placebo OIT for 8 weeks followed by omalizumab plus placebo OIT for 44 weeks. In total, participants complete 52 weeks of active multiallergen or placebo OIT.

Each participant who tolerates at least 9 mg of protein of multiallergen or placebo OIT during an initial dose escalation (IDE) visit will enter a build-up phase for up to 24 weeks to reach a maximum maintenance dose of 1000 mg of protein of each of their 3 participant-specific foods (ie, for a total maximum dose of 3000 mg of protein or 3000 mg of placebo OIT). Each participant who reaches a minimum total maintenance dose of 750 mg of

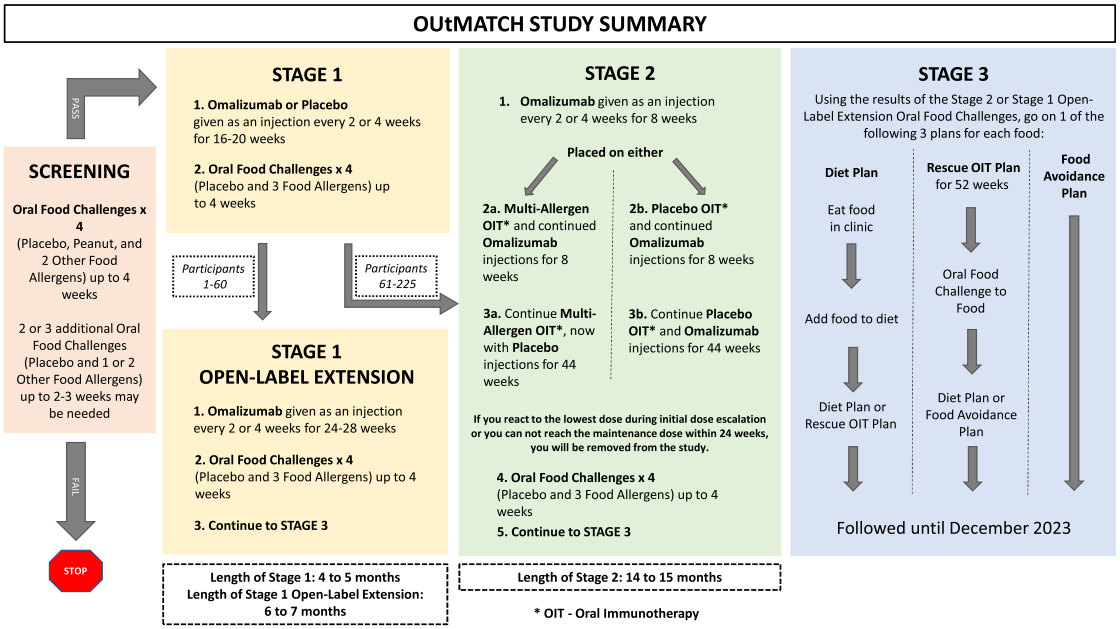

FIG 1. Study summary schematic.

protein (equivalent to 250 mg of protein of each of their 3 participant-specific foods) within 24 weeks of completing the IDE will continue to receive this dose during the maintenance phase. At the end of the 52-week treatment period, each participant will complete a DBPCFC to each of their 3 foods and placebo, for a cumulative dose of 8044 mg of protein of each food. The assigned treatment will continue until the DBPCFC has been completed. Each participant who completes stage 2 will move to stage 3 of the study.

In stage 3, following completion of treatment and the DBPCFC in the stage 1 OLE or stage 2, each participant will receive an individualized treatment plan for peanut and each of the 2 other participant-specific foods based on the results of their DBPCFC in the stage 1 OLE or stage 2. The treatment plan may include any combination of the following: long-term follow-up with dietary consumption of a food, long-term follow-up with avoidance of a food, and rescue OIT for a food. The treatment plan for each food may change throughout stage 3 depending on the participant's preferences and response to treatment. The duration of stage 3 ranges from a minimum of 12 months to as long as 36 months for participants enrolled earlier in the trial. Stage 3 is not hypothesis-driven; rather, it provides an opportunity to study long-term outcomes that may help to inform future clinical practice.

Rationale for selection of the investigational products

The rationale for the proposed study interventions in this protocol is based on substantial preliminary data regarding both approaches: omalizumab as monotherapy and as an adjunct to OIT.[9-18] In stage 1, monotherapy with omalizumab will be compared with placebo to test the hypothesis that omalizumab can increase oral food challenge (OFC) reactivity thresholds in a clinically significant manner. In stage 2, longer-term treatment with omalizumab (combined with placebo OIT) will be compared with active multiallergen OIT initiated under the protection of open label omalizumab. Although omalizumab has been shown to improve the safety of OIT,[9,10,12] no studies have directly compared these 2 treatment approaches. This comparison will be important to the design of future studies, as well as to the potential use of these approaches in clinical practice. Study participants will then proceed to stage 3, in which we will study the possibility that these treatments will allow for introduction of the allergenic foods into the diet, a practice that has been used informally in prior studies and clinical practice but has never been addressed in a systematic manner. Whatever the outcomes, the study will provide groundbreaking data that will affect the future of treatment for both peanut allergy and multifood allergy. Further, as described in the following sections, the safety and efficacy of these treatments in patients as young as age 1 year will be studied, which is another groundbreaking advance in the study of potential treatments for food allergy.

Rationale for study population

This study will enroll children and adults who are aged 1 year to younger than 56 years and have multifood allergies. The rationale for choosing patients with multifood allergies lies in the fact that so many patients have allergy to multiple foods and that the value of treatment approaches focusing on a single food, such as peanut OIT, is inherently limited. The second major rationale for this study population is related to age, with studies suggesting that treatment of peanut allergy with oral and/or epicutaneous immunotherapy may be more efficacious, and equally safe, when initiated in younger children.[6,19] This study will therefore expand our knowledge regarding the effects of OIT in children as young as 1 year, but this time focusing on children with allergy to multiple other foods in addition to peanut. Further, it will provide a unique opportunity to study the effects of omalizumab, both as monotherapy and as an adjunct to OIT, in younger

TABLE I. Inclusion and exclusion criteria

Inclusion criteria

1. Participant and/or parent or legal guardian must be able to understand and provide informed consent and/or assent, as applicable
2. Male or female, aged 1 y to <56 y at screening
3. In the case of peanut allergy, the participant must meet all of the following criteria to minimize the chance that the he or she will develop natural tolerance to peanut over the course of the study
   a. Positive result of skin prick test to peanut (wheal ≥4 mm larger than the saline control)
   b. Positive peanut IgE level (≥6 kUA/L) at screening or within 3 mo of screening, as determined by ImmunoCap
   c. Positive blinded OFC to peanut during the screening DBPCFC, defined as experiencing dose-limiting symptoms at 1 dose of ≤100 mg of peanut protein
4. Allergy to ≥2 of the other 6 foods (milk, egg, wheat, cashew, hazelnut, and walnut), with allergy to milk and egg defined as the inability to tolerate both cooked and uncooked forms; each participant must meet all of the following criteria for ≥2 of the other 6 foods to minimize the chance that the participant will develop natural tolerance to ≥2 of the 6 other foods over the course of the study
   a. Milk, egg, or wheat
      i. Positive result of skin prick test to the study food (wheal ≥4 mm larger than the saline control)
      ii. Positive result of test for food specific–IgE level (≥6 kUA/L) at screening or within 3 mo of screening, as determined by ImmunoCap
      iii. Positive result of blinded OFC to food during the screening DBPCFC, defined as experiencing dose-limiting symptoms at 1 dose of ≤300 mg of food protein
   b. Cashew, hazelnut, or walnut
      i. Positive result of skin prick test to food (wheal ≥4 mm larger than that of the saline control) *or* positive food specific–IgE level (≥6 kUA/L) at screening or within 3 mo of screening, as determined by ImmunoCap
      ii. Positive result of blinded OFC to food during the screening DBPCFC, defined as experiencing dose-limiting symptoms at 1 dose of ≤300 mg of food protein
5. With body weight (as measured at screening) and total serum IgE level (as measured within 3 mo of screening) suitable for omalizumab dosing
6. If the participant is a female of child-bearing age, she must have a negative urine or serum pregnancy test
7. In the case of a woman with childbearing potential, she must agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods (barrier methods or oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception with comparable efficacy) during the treatment period and for 60 d after the last dose of study drug
8. Participants must plan to remain in the study area of an OUtMATCH clinical research unit during the trial
9. Participants must be willing to be trained on the proper use of an epinephrine autoinjector and be willing to provide an epinephrine autoinjector for the duration of the study

Exclusion criteria

1. Inability or unwillingness of a participant and/or parent or legal guardian to give written informed consent and/or assent or comply with the study protocol
2. Clinically significant laboratory abnormalities at screening
3. Dose-limiting symptoms during the blinded OFC in response to placebo during the screening DBPCFC
4. Sensitivity or suspected or known allergy to any ingredients (including excipients) of the active or placebo OFC material, multiallergen OIT, or drugs related to omalizumab (eg, mAbs, polyclonal gamma globulin). Guidance for determination of sensitivity to excipients will be detailed in the manual of procedures
5. Poorly controlled atopic dermatitis at screening, per the principal investigator's discretion
6. Poorly controlled or severe asthma and/or wheezing at screening, defined by ≥1 of the following criteria
   a. Criteria listed in the latest asthma control guidelines from to the Global Initiative for Asthma (see Appendix 3)
   b. History of ≥2 courses of systemic corticosteroids within 6 mo of screening or 1 course of systemic corticosteroids within 3 mo of screening to treat asthma and/or wheezing
   c. Prior intubation and/or mechanical ventilation for asthma and/or wheezing
   d. One hospitalization or emergency department visit for asthma and/or wheezing within 6 mo of screening
   e. FEV_1 value < 80% of predicted or ratio of FEV_1 value to forced vital capacity of <75%, with or without controller medications (only for participants who are aged ≥7 y and able to undergo spirometry)
   f. Daily inhaled corticosteroid dosing of >500 μg of fluticasone (or an equivalent inhaled corticosteroid based on the CoFar inhaled corticosteroid equivalency tables)
7. History of severe anaphylaxis in response to participant-specific foods that will be used in this study, defined as neurologic compromise or requiring intubation
8. Treatment with a burst of oral, intramuscular, or intravenous steroids for >2 d for an indication other than asthma and/or wheezing within 30 d of screening
9. Currently receiving oral, intramuscular, or intravenous corticosteroids; tricyclic antidepressants; or β-blockers (oral or topical)
10. Past or current eosinophilic gastrointestinal disease within 3 y of screening
11. Past or current cancer, or currently being investigated for possible cancer
12. Previous adverse reaction to omalizumab
13. History or current use of any immunotherapy for any of the foods being examined in this study (eg, OIT, sublingual immunotherapy, epicutaneous immunotherapy) within 6 mo of screening
14. Treatment with mAb therapy, such as omalizumab, dupilumab, benralizumab, mepolizumab, reslizumab, or other immunomodulatory therapy within 6 mo of screening
15. Currently in the "build-up phase" of inhalant allergen immunotherapy (ie, maintenance dosing has not yet been reached); individuals tolerating maintenance allergen immunotherapy can be enrolled
16. Inability to discontinue taking antihistamines for the minimum washout periods required for skin prick tests or OFCs
17. Current participation in another therapeutic or interventional clinical trial or participation within 90 d of screening
18. Use of investigational drugs within 24 wk of screening
19. Pregnant or breast-feeding, or intending to become pregnant during the study or within 60 d after the last dose of omalizumab or placebo for omalizumab
20. Has a first-degree relative already enrolled in the study
21. Past or current medical problems (eg, severe latex allergy); history of other chronic diseases (other than asthma and/or wheezing, atopic dermatitis, or rhinitis) requiring therapy (eg, heart disease, diabetes); findings from physical assessment, or abnormalities in clinical laboratory testing results that are not listed but in the opinion of the principal investigator, may pose additional risks resulting from participation in the study, interfere with the participant's ability to comply with study requirements, or affect the quality or interpretation of the data obtained from the study

children, as thus far, it has not been studied in children younger than 2 years.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are detailed in Table I. In brief, the study includes individuals aged 1 year to 55 years who have peanut allergy and allergy to at least 2 of the other 6 protocol-defined foods (milk, egg, wheat, cashew, hazelnut, and walnut). Potential participants must have a body weight and total serum IgE level suitable for omalizumab dosing (see Fig E1 in the Online Repository at www.jaci-global.org). Key exclusion criteria include poorly controlled or severe asthma, a history of severe anaphylaxis in response to participant-specific foods, a history of eosinophilic gastrointestinal disease within 3 years of screening, and immunotherapy for any of the foods being treated in this study or treatment with mAb therapy within 6 months of screening.

RESULTS

Study end points

The study end points are described in detail in Table II. The primary end point is consumption of a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of stage 1 (for OFC dosing, see Table E1 in the Online Repository at www.jaci-global.org). Key secondary end points include consumption of a single dose of more than 1000 mg of cashew, milk, or egg protein without dose-limiting symptoms during the DBPCFC at the end of stage 1, as well as consumption of at least 1 dose of 2000 mg of protein of all 3 foods without dose-limiting symptoms during the DBPCFC at the end of stage 2 (this is the primary end point for stage 2) and in stage 3 to compare dietary consumption of foods after the conclusion of stage 1 OLE or the 2 treatment arms of stage 2.

Individual and study stopping rules

For the individual and overall study stopping rules, see Tables E4 and E5, respectively (available in the Online Repository at www.jaci-global.org). Key stopping rules for individual participants include pregnancy, any CoFAR grade 4 allergic reaction related to omalizumab/placebo or multiallergen OIT/placebo OIT, or biopsy-documented eosinophilic esophagitis (EoE). The CoFAR Grading Scale for Systemic Allergic Reactions, version 3.0, is presented in Table E6 (in the Online Repository at www.jaci-global.org).

The study stopping rules include the following: any death related to OIT dosing, OFC, omalizumab, or placebo for omalizumab; more than 3 participants requiring more than 2 injections of epinephrine during a single OIT dosing; more than 1 participant requiring more than 2 injections of epinephrine during a single omalizumab or placebo injection; more than 1 participant with more than 1 CoFAR grade 4 adverse event (AE) related to OIT dosing; more than 3 CoFAR grade 4 AEs related to OFC; and 5% or more of the enrolled participants having been diagnosed with biopsy-proved EoE, as assessed on a rolling basis during regular AE reviews, and the total number of cases of EoE equaling 5 or more.

If any of the aforementioned overall study stopping rules are met, study enrollment will be suspended, IDE visits will be suspended, dose escalation during OIT build-up will be stopped, and all enrolled participants in stage 2 or stage 3 will continue to receive their current dose of OIT pending expedited review of all pertinent data by the National Institute of Allergy and Infectious Diseases (NIAID), Division of Allergy, Immunology and Transplantation (DAIT) Data and Safety Monitoring Board. Depending on the stopping rule, additional study procedures (see Table E5) will also be suspended pending expedited review of all pertinent data.

Treatment description

Omalizumab is a recombinant humanized mAb that binds to the FcεRI binding epitope of human IgE, preventing human IgE from binding to its specific high-affinity receptors on mast cells and basophils. Omalizumab is approved by the US Food and Drug Administration and the European Commission for the treatment of moderate-to-severe asthma in patients aged 6 years or older, chronic idiopathic urticaria in patients aged 12 years or older, and nasal polyps in patients aged 18 years or older. Omalizumab is not approved for treating food allergy. The composition of the placebo is the same as that of the active study drug without the omalizumab. Omalizumab and placebo are administered as a subcutaneous injection and will be dosed at the clinical sites according to the omalizumab dosing table (see Fig E1).

The multiallergen OIT consists of some combination of peanut, milk, egg, wheat, cashew, hazelnut, and/or walnut. The placebo OIT consists of oat flour. The multiallergen OIT and placebo OIT are manufactured by the Sean N. Parker Center for Allergy and Asthma Research within Stanford University (Mountain View, Calif) and packaged and labeled by the DAIT/NIAID Clinical Product Center, EMINENT Services Corporation (Fredrick, Md). The dosing schedule for IDE for multiallergen OIT or placebo OIT is displayed in Table E2 (in the Online Repository at www.jaci-global.org), beginning with 3 mg of protein of each food and with a maximum possible dose of 375 mg of each food (1125 mg in total).

The multiallergen OIT dose build-up begins at the last dose that the participant was able to tolerate on the IDE visit (range 9 mg to 1125 mg of total allergen) (see Table E3 in the Online Repository at www.jaci-global.org). Dose build-up occurs every 2 weeks until a maximum dose of 1000 mg of each allergen (3000 mg total) has been reached. Participants are required to reach a minimum dose of 250 mg of each allergen (cumulative dose 750 mg) to continue through stage 2. Treatment options in stage 3 include long-term follow-up with dietary consumption of a food or rescue OIT for 1 or more foods. A third option, namely, long-term follow-up with avoidance of 1 or more foods, can be utilized based either on patient preference or difficulty tolerating 1 or more foods. The treatment plan for each food may change during stage 3 depending on a participant's goals and response to treatment. Dietary consumption of a food is an option for all participants who tolerate at least 600 mg of a food on their exit DBPCFC from the stage 1 OLE or stage 2. This option is initiated through an initial open feeding of the food, after which each participant is provided with a detailed plan of food equivalents that can be used to provide his or her minimum or maximum daily dose. If the participant receives rescue OIT for the food immediately after completing the stage 1 OLE or stage 2, he or she will either have an IDE visit or proceed directly to dose build-up depending on the results of the DBPCFC at the end of the stage 1

TABLE II. Study end points

The primary end point is consumption of 1 dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of stage 1

Key secondary end points

Stage 1

- Consumption of 1 dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of stage 1
- Consumption of 1 dose of ≥1000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of stage 1
- Consumption of 1 dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of stage 1

Stage 2

- Consumption of ≥1 dose of 2000 mg protein of all 3 foods without dose-limiting symptoms during the DBPCFC at the end of stage 2. This is the primary end point for stage 2

Other secondary end points

- Consumption of 1 dose of ≥600 mg, 1 dose of ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food, ≥2 foods, or all 3 foods without dose-limiting symptoms during the DBPCFC at the end of stage 1 (except for those end points already defined by the primary and key secondary end points in stage 1)
- Number of foods consumed at 1 dose of ≥600 mg, 1 dose of ≥1000 mg, ≥1 dose of 2000 mg, or 2 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of stage 1
- Consumption of 1 dose of ≥600 mg, 1 dose of ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, ≥2 foods, or all 3 foods without dose-limiting symptoms during the DBPCFC at the end of stage 2 (except for the end point already defined by the primary end point for stage 2)
- Number of foods consumed at a 1 dose of ≥600 mg, 1 dose of ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of stage 2
- Number of weeks in each 3-wk period during stage 3 during which ≥300 mg protein of each food is consumed at least twice per wk
- Number of weeks in each 8-wk period during stage 3 during which each food is not consumed

Safety end points

- An AE related to the study therapy regimen received during stage 1
- An AE related to the study therapy regimen received during the stage 1 OLE
- An AE related to the study therapy regimen received during stage 2
- An AE related to oral food intake received during stage 3

Exploratory end points

- Percentage of change in the maximum dose of food protein consumed without dose-limiting symptoms during the DBPCFC at the end of stage 1 and during the DBPCFC at the end of stage 2
- Consumption of 1 dose of ≥600 mg, 1 dose of ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food, ≥2 foods, or all 3 foods without dose-limiting symptoms during the DBPCFC at the end of the stage 1 OLE
- Number of foods consumed at 1 dose of ≥600 mg, 1 dose of ≥1000 mg, ≥1 dose of 2000 mg, ≥2 doses of 2000 mg, or 3 doses of 2000 mg protein of each food without dose-limiting symptoms during the DBPCFC at the end of the stage 1 OLE
- Change in quality of life between wk 0 in stage 1 and the following times
  - First DBPCFC visit at the end of stage 1
  - For those participants who move to the stage 1 OLE
    - First omalizumab injection visit in the stage 1 OLE
    - First DBPCFC visit at the end of the stage 1 OLE
    - Last DBPCFC visit at the end of the stage 1 OLE
  - For those participants who move to stage 2
    - First omalizumab injection visit in stage 2
    - First DBPCFC visit at the end of stage 2
    - Last DBPCFC visit at the end of stage 2
  - 6 mo after beginning stage 3

Pharmacokinetic end points

- Omalizumab trough concentration, measured at the following times
  - First screening DBPCFC visit
  - First DBPCFC visit at the end of stage 1
  - First DBPCFC visit at the end of the stage 1 OLE (for those participants who move to the stage 1 OLE)
  - IDE visit during stage 2 (for those participants who move to stage 2)
  - First DBPCFC visit at the end of stage 2 (for those participants who move to stage 2)

Biomarker end points

- Total IgE level
- Total free IgE level
- Allergen-specific IgE level
- Allergen-specific IgG4 level
- Allergen-specific IgA level
- Ratio IgG4 level to IgE level
- Basophil activation
- Skin prick test results

(Continued)

TABLE II. *(Continued)*

These Immune biomarkers will be measured at the following times
● First screening DBPCFC visit
● First DBPCFC visit at the end of stage 1
● First DBPCFC visit at the end of the stage 1 OLE (for those participants who move to stage 1 OLE)
● IDE visit during stage 2, except the skin prick test results, total IgE level, and allergen-specific IgE level (for those participants who move to stage 2)
● Initial maintenance dose visit during stage 2, except the skin prick test results, total IgE level, and allergen-specific IgE level (for those participants who move to stage 2)
● First DBPCFC visit at the end of stage 2 (for those participants who move to stage 2)
● Six mo after the beginning of stage 3
Additional mechanistic end points will be measured at the following times
● First screening DBPCFC visit
● First DBPCFC visit at the end of stage 1
● IDE visit during stage 2 (for those participants who move to stage 2)
● Initial maintenance dose visit during stage 2 (for those participants who move to stage 2)
● First DBPCFC visit at the end of stage 2 (for those participants who move to stage 2)

OLE or stage 2. The IDE and dose build-up will proceed as already described for stage 2.

Stratification, randomization, and blinding

Randomization is accomplished through a password-protected, web-based, randomization system maintained by the DAIT Statistical and Clinical Coordinating Center at Rho Federal Systems Division, Inc (Durham, NC). Participants who meet the eligibility criteria are randomized to receive omalizumab or placebo using a 2:1 allocation ratio and a permuted block randomization scheme stratified on the basis of age younger than age 6 years at randomization and milk as a participant-specific food (yes/no). Participants who move to stage 2 are rerandomized to omalizumab-facilitated OIT or omalizumab plus placebo OIT using a 1:1 allocation ratio and a permuted block randomization scheme stratified on the basis of stage 1 treatment arm. The order of the blinded OFC to peanut during each DBPCFC is also randomized.

Participants, parents and legal guardians, and clinical research unit staff who do not administer omalizumab or placebo injections will be blinded to treatment arm in stage 1 and 2 until all participants have completed stage 3 and the database has been locked.

Statistical analysis plan and sample size considerations

Analysis for stage 1. The primary analysis of the primary end point will use a logistic regression model to estimate the odds ratio (and associated 95% Wald CIs) comparing consumption of a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of stage 1 between the omalizumab and placebo arms. Fixed effects will include only the treatment arm, age at randomization (<6 years vs ≥6 years), milk as a participant-specific food (yes/no), and the order of the blinded OFC to peanut during the DBPCFC at the end of stage 1. The analysis of each of the key secondary end points will use a similar approach. Analyses of the primary and key secondary end points will be based on 2-sided superiority tests. To control the inflation of type I error that arises when multiple tests of comparison are performed within and across multiple families of end points (ie, the primary end point as well as key secondary end points), both gatekeeping and multiple testing strategies will be performed to ensure that the overall family-wise error rate is less than 5%.

Sample size and power calculations for the primary end point in stage 1. A total of 225 participants (150 receiving omalizumab and 75 receiving placebo instead of omalizumab) will be randomized in stage 1. It is expected that 210 of those participants will be younger than 18 years, with at least 50 of them aged 1 year to less than 6 years. Power calculations for this end point were performed using Fisher exact tests with a 2-sided type I error rate of 5%. Table E7 (available in the Online Repository at www.jaci-global.org) provides the estimated power to detect an odds ratio of consuming a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of stage 1 between the omalizumab and placebo arms. For example, assuming that 10% of participants randomized to placebo in stage 1 and 70% of participants randomized to omalizumab in stage 1 consume a single dose of at least 600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of stage 1, a sample size of 210 participants (140 receiving omalizumab and 70 receiving placebo for omalizumab) will provide more than 99% power to detect an odds ratio of 21.0.

Power calculations for the key secondary end points in stage 1. Assuming that the percentages of the participants with cashew, milk, and egg as participant-specific foods are 59%, 30%, and 27%, respectively, and 10% of the participants randomized to placebo consume a single dose of at least 1000 mg of protein of each food without dose-limiting symptoms, these prevelences will provide a sample size with 80% power to detect odds ratios for consumption of at least 1000 mg of each food between arms of 4.5, 7.5, and 8.3, respectively, with use of Fisher exact tests with a 2-sided type I error rate of 5% (see Table E8 in the Online Repository at www.jaci-global.org).

Sample size and power calculations for the primary end point in stage 2. To move to stage 2, participants must complete stage 1. Assuming that approximately 10% of the 210 participants younger than 18 years do not complete stage 1 and 60 participants younger than 18 years move into stage 1 OLE, it is expected that 128 participants younger than 18 years will be randomized in stage 2. With the stage 2 primary end point defined as successful consumption of at least 1 dose of 2000 mg of protein of all 3 foods by using a 2-sided Fisher exact test with

a type I error rate of 5% and assuming that 60% of participants randomized to omalizumab plus placebo OIT and 85% of participants randomized to omalizumab-facilitated OIT will successfully consume at least 1 dose of 2000 mg of protein of all 3 foods (resulting in an odds ratio of 3.8), a sample size of 128 (64 per arm) will provide 86% power to detect this odds ratio.

DISCUSSION

This study represents a unique collaboration between the NIAID (through CoFAR) and industry (Genentech and Novartis), with all parties committed to the advancement of treatment for food allergy. In 2018, Genentech was granted breakthrough therapy designation for omalizumab for the prevention of severe allergic reactions following accidental exposure to 1 or more foods in people with allergies. Although the potential value of this therapy will remain in question until this study has been completed, we are optimistic that the study will provide a critical step toward the approval of another treatment for food allergy —this time focused not on a single food allergen (peanut) but rather on the full spectrum of severe food allergies. Further, the data obtained in stages 2 and 3 will provide further direction toward future treatment options for food allergy.

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